UNDERSTANDING THE MECHANISM OF TRICUSPID ANNULOPLASTY SUTURE DEHISCENCE

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UNDERSTANDING THE MECHANISM OF TRICUSPID ANNULOPLASTY SUTURE DEHISCENCE

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I would like to dedicate this thesis to my mother, father and sister.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF SYMBOLS AND ABBREVIATIONS

FTR	Functional Tricuspid Regurgitation
RA	Right Atrium
ROI	Region of Interest
RV	Right Ventricle
TV	Tricuspid Valve

ABSTRACT

Functional tricuspid regurgitation is commonly repaired by ring annuloplasty. Suturing an annuloplasty ring into the tricuspid valve presents the potential for annular suture dehiscence (tear-out from the tissue) due to the cyclic forces applied by cardiac contraction. Dehiscence has been noted clinically across multiple studies examining TR repair by ring annuloplasty, primarily at the septal region of the annulus. Analysis of the tricuspid microstructure can support the development of improved implantation procedures to account for a potential lack of structural support in regions of the annulus. This study consists of 2 complimentary experiments aimed to understand the mechanism of suture dehiscence at the macro and micro levels. In the first, the tricuspid annulus suture holding strength was studied as a function of position. Tricuspid valves (N=15) were excised from ovine hearts and suture pullouts were conducted at 12 annular positions. In the second, relative collagen density at 6 suture passage sites around the annulus was quantified via autofluorescence microscopy, using a second cohort of valves (N=4). The highest pullout forces were experienced around the septal region of the annulus (e.g. septal leaflet vs. all other positions: 8.70 ± 3.14 N vs. 5.70 ± 1.94, $p<0.0001$), peaking at the middle of the septal leaflet (10.00 ± 4.07 N). This region also demonstrated the highest normalized collagen density, with a significant reduction at the anterior-posterior commissure, the posterior leaflet midpoint, and the posterior-septal commissure (each $p<0.05$ vs. septal leaflet). Taking this data together with the clinical predominance of dehiscence at the septal leaflet, it is believed that while a higher force is required to displace septal sutures, such higher forces must indeed occur *in vivo*. The ventricular septum is uniquely situated in a position that is subject to loading from both

sides of the heart. The fibrous trigone present at the septum reduces the compliance of this region as a whole. Before these findings can be safely applied to inform novel ring designs or implantation practices, animal studies are necessary to discern how this dehiscence occurs *in vivo*.

CHAPTER 1

INTRODUCTION AND LITERATURE REVIEW

Tricuspid Valve Anatomy

The tricuspid valve (TV) of a typical 4-chambered heart maintains unidirectional blood flow between the right atrium and the right ventricle.[1] This valve is composed of three leaflets: the anterior, posterior, and septal. Chordae tendineae attach the leaflets to three papillary muscles, located beneath the commissures (junctions) between each of the leaflets.[1] In atrial systole, the chordae are relaxed because blood is being forced down a pressure gradient from the atrium into the ventricle. During ventricular systole, the increased blood pressure in the ventricular chamber causes the valve to shut to prevent regurgitation. Additionally, as seen in figure 1.1, the right fibrous body (also referred to as the trigone) of the heart is located near the septal leaflet and provides additional structure and support to the valve. The tricuspid annulus is primarily composed of myocardium and collagen fibers.[2]

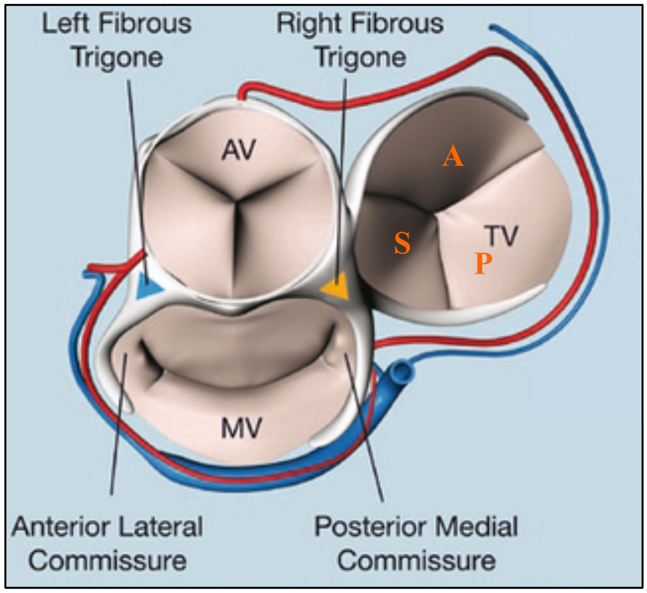

Figure 1.1. Basic Tricuspid Valve Anatomy.[3] The image shows anatomically where the tricuspid valve is in relation to the aortic and mitral valves, viewed superiorly. The mitral and tricuspid valves share a trigone, which provides structural support to the septum of the heart. The anterior tricuspid leaflet is typically the largest of the leaflets, and the posterior is the smallest. A= anterior leaflet. P = posterior leaflet. S = septal leaflet.

Functional Tricuspid Regurgitation Pathology and Treatment

Functional tricuspid regurgitation (FTR), refers to tricuspid regurgitation (blood leaking backwards into the right atrium) due to annular dilation caused by geometric distortion of the TV anatomy,[5] originating from left-sided heart disease or right ventricular volume and pressure overload.[6] The region of leaflet coaptation is lost[5], primarily as the result of either leaflet prolapse or elongation of the chordae over time.[7] Subsequently, this leads to dyspnea, fatigue, and in extreme cases death. Echocardiography is typically used to diagnose potential TR[8].

Valve repair (preferred over valve replacement, when possible)[9] to treat FTR typically involves the implantation of an annuloplasty ring.[10] The ring acts as an artificial annulus for the leaflets, pulling the leaflets together and reducing the annular circumference to restore adequate leaflet coaptation.[11] A study at Toronto General

Hospital observed 702 TV repair patients, of which 493 had no annuloplasty ring and 209 did. The study concluded that the use of an annuloplasty ring promoted longevity over patients who did not receive the device. The 15-year post-treatment survival rate increased in ring annuloplasty patients ($p=0.03$), with complications of recurrent FTR and unintended tearing of sutures.[12]

Suture Dehiscence

Sutures holding annuloplasty rings in the tricuspid annulus must be able to withstand forces from the cyclic contractions of the heart without dehiscing (tearing out from the tissue).[13] Incidences of ring dehiscence were found in a retrospective analysis of 820 TV ring-implant patients (rigid rings, 8.7% vs. flexible rings, 0.9%), almost exclusively occurring at the TV septal region.[14] Flexible bands used to treat FTR have shown advantages in reducing the risk of dehiscence; however, rigid rings are sometimes preferred due to their sustained effects for maintaining stable postoperative regurgitation grades.[15] This study supports the need for a more comprehensive understanding of the associated annular tissue mechanics and their variation across the annular circumference.[14]

A study conducted over 60 porcine mitral valves evaluated the holding strength of mattress sutures that were put under controlled tension until they tore through the tissue using multiple suture techniques. Superiority of a suture technique was not established; the main point of concern as determined via histological analysis was the direction of the suture in relation to the direction of the collagen fibers.[16] To understand the mechanism of dehiscence, it is important to understand the tensile mechanical properties of the tricuspid valve annulus, in terms of both macro and microstructure.

Tricuspid Annulus Microstructure

The annulus of the tricuspid valve contains a myocardial collagen matrix. Fibrillar collagen (types I, II, III, IV) connects to cardiomyocytes. Collagen types I and II provide resistance to tension and intermittent pressure, respectively.[17] Type III collagen provides structural maintenance in organs that expand, and type IV collagen anchors layers holding groups of cells together.[17] When a suture is run through this matrix, the collagen is expected to provide anchorage for the suture and prevent dehiscence.

A study performed to characterize mitral valve annular strength under circumferential stretch found that the bulk of this strength comes from collagen content. Histological analysis of the mitral valve revealed a positive correlation between tissue stiffness and collagen content.[18] A similar trend in collagen content may be seen across the circumference of the tricuspid valve.

Understanding the Mechanism of Dehiscence

The incidence of dehiscence can be characterized by annular region. With regards to the more extensively studied mitral valve, current research efforts are exploring the implications of mitral annuloplasty ring shape, size, and stiffness on the risk of ring dehiscence.[19,20] These same risk factors apply in the case of tricuspid annuloplasty. An improved understanding of the strongest and weakest regions of the tricuspid annulus may support the design of next-generation devices and/or implantation techniques that reduce dehiscence risk.

Objectives

This study aims to understand the mechanism of suture dehiscence for tricuspid annuloplasty rings. The approach taken to evaluate this mechanism includes:

1) Suture pullout tests to measure the force necessary to induce dehiscence.
2) Autofluorescence analysis of 6 annular positions (green positions of figure 3.1) to quantify collagen density present at each region of the valve.

Based on the clinical experience, it was hypothesized that **the lowest pullout forces and the lowest collagen content are found near the septal region of the annulus.**

CHAPTER 2

MATERIALS AND METHODS

Annulus Notation

For the purposes of this study, positions around the tricuspid annulus are referred to as shown in figure 3.1.

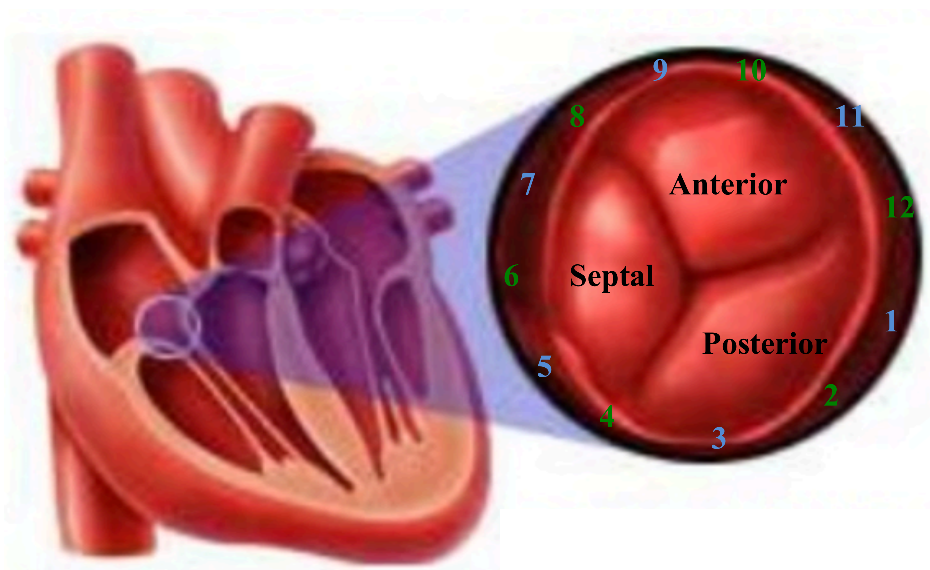

Figure 3.1. Tricuspid Valve Notation for Experimentation.[21] Positions 4, 8 and 12 represent the commissures of the valve. Positions 2, 6 and 10 represent the annular midpoint of each leaflet. The positions labeled in green were tested for collagen quantification and all 12 points were used for suture pullout testing.

The right fibrous trigone (figure 1.1) is typically found near position 6 (figure 3.1), bordering the tricuspid valve and the aortic wall.

Suture Pullout Experimentation

Fresh ovine hearts (N=15) were kept at 4°C during storage (never frozen) and all sample testing was performed at room temperature. Tricuspid valves were excised and mounted to a custom-made plate for uniaxial testing. Continuous running sutures were placed around inner and outer edges of the annulus. Annuloplasty guidelines were followed when running the test sutures through their respective positions on the valves, including insertion 1-2mm above the hinge line, a 10mm width between the entrance and exit points of the suture, and a 10° angle between needle and leaflet hinge.[22] Twelve Y-31 2-0 Ti·Cron sutures (Covidien, UK) were used as test sutures through the intended positions (figure 3.1). The mounting plate was next attached to an ElectroForce 3200 uniaxial tester (Bose Corporation, Eden Prairie, MN). The plate had two degrees of freedom, allowing the point of interest to align directly beneath the uniaxial testing arm.[19] The upper arm (figure 3.2) was then prescribed to move at 0.2mm/s over a range of 13.2mm total. Force was recorded using a 25N load cell (SMT1-22; Interface, Scottsdale, AZ). To ensure the suture would tear out before the tester reached maximum displacement, the mounting plate was lowered to induce 1N of tension in the suture at the start of the test. Once the suture dehisced, the test ended, and the same procedure was repeated for each subsequent point (N=12, figure 3.1). The valves were sprayed lightly with water every 2 minutes to avoid dehydration. The same operator mounted all valves and inserted all test sutures in order to minimize potential inconsistencies.

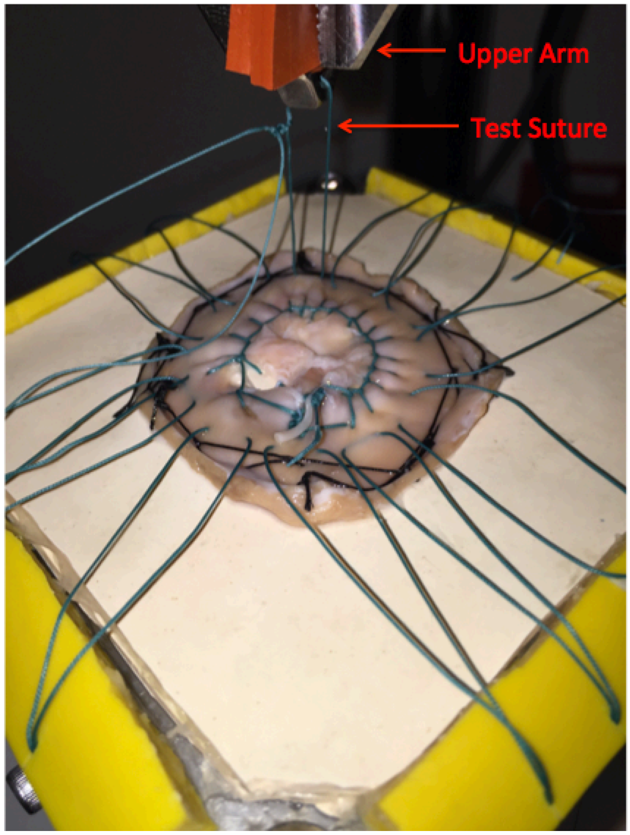

Figure 3.2 Suture Pullout Test Setup. Shown are sutures placed in their 12 respective annular positions. The current position being tested is connected to the upper testing arm and the sutures not in use are harnessed lightly to the plate.

The data obtained was later mapped to the collagen data to assess whether an increase in collagen content is directly linked to an increase in the pullout force necessary for dehiscence. All statistical analysis was conducted in Minitab 17 (Minitab Inc, State College, PA), except for ANOVA, which was performed in OpenBUGS[23] (OpenBUGS Foundation, Helsinki, Finland).

Collagen Characterization

Tricuspid valves (N=4) were sectioned at 6 annular positions (green positions in figure 3.1). These segments of tissue were paraffinized, sectioned to 20µm slices, and deparaffinized according to standard procedures. Two-photon excitation microscopy was used for sample imaging, using their own native autofluorescence. The samples were imaged at a 10X objective, with an 800nm excitation wavelength. Collagen was detected at 390-420nm and non-specific fibrous structures were detected at 485-700nm. For each valve, the operator optimized the settings for the brightest of all six samples. Acquisition settings were then held constant for all positions across the valve to allow image comparison.

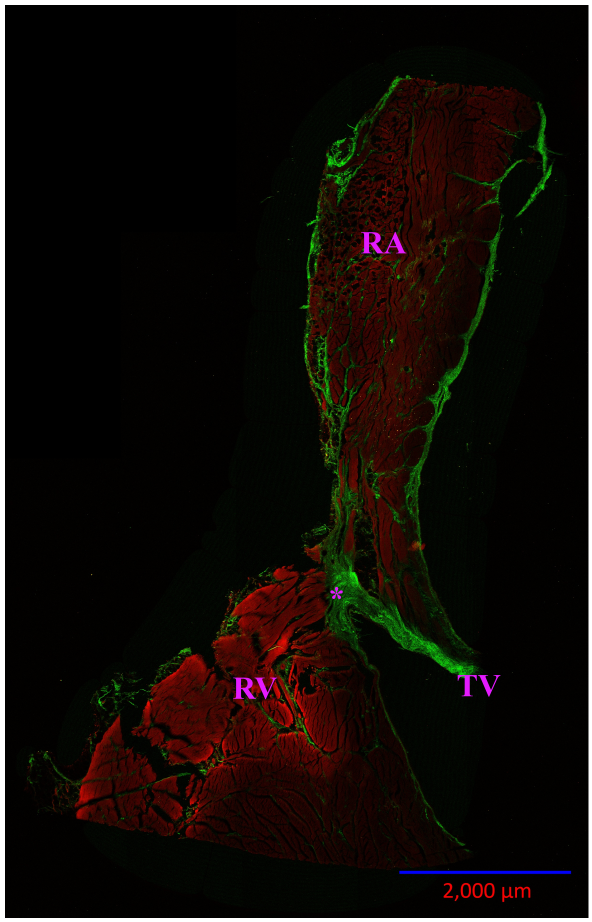

Figure 3.3. Sample Image of Autofluorescence Results. This image shows an anterior leaflet midpoint. Green indicates collagen presence, and red indicates non-specific fibers. RA = right atrium. RV = right ventricle. TV = tricuspid valve. * = hinge point.

To quantify the presence of collagen, Matlab was used to determine the mean pixel intensity for each color over a 2mm x 3mm region of interest (ROI). One corner of the ROI was fixed to the leaflet hinge point, and the long edge of the ROI ran along the endocardial surface. These dimensions allowed for a 1mm buffer region around the suture passage area based on prescribed suture implantation parameters.[22] As the collagen or non-specific fiber density of a pixel increased, the associated pixel intensity value increased towards 255 and thus contributed more to the sample's mean pixel intensity.

CHAPTER 3

RESULTS

Suture Pullout Testing Results

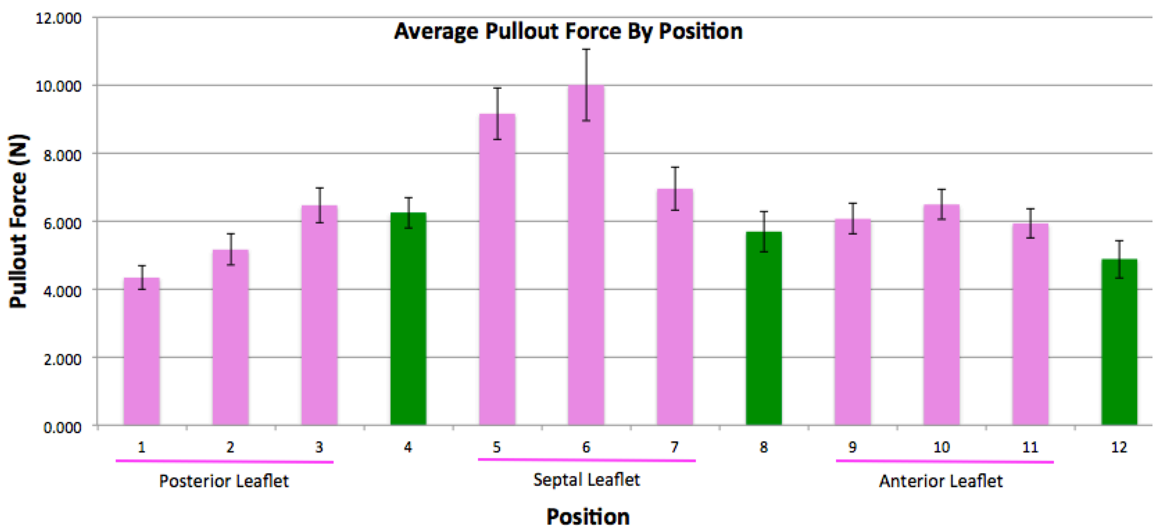

Figure 4.1. Suture Pullout Force By Position. The x-axis represents the positions shown in figure 3.1. The green bars denote the commissural points. Shown: mean ± standard error.

An average force of 6.45 ± 2.17N was necessary to induce suture dehiscence. Position 6 showed the greatest pullout force (10.00 ± 4.07 N) and position 1 showed the lowest (4.34 ± 1.33N). Subdividing the valve by leaflets and commissures revealed that the septal annulus required the highest pullout force (8.70 ± 3.41N) of any region. The average pullout force at each commissure was found to be lower than its 2 respective adjacent positions.

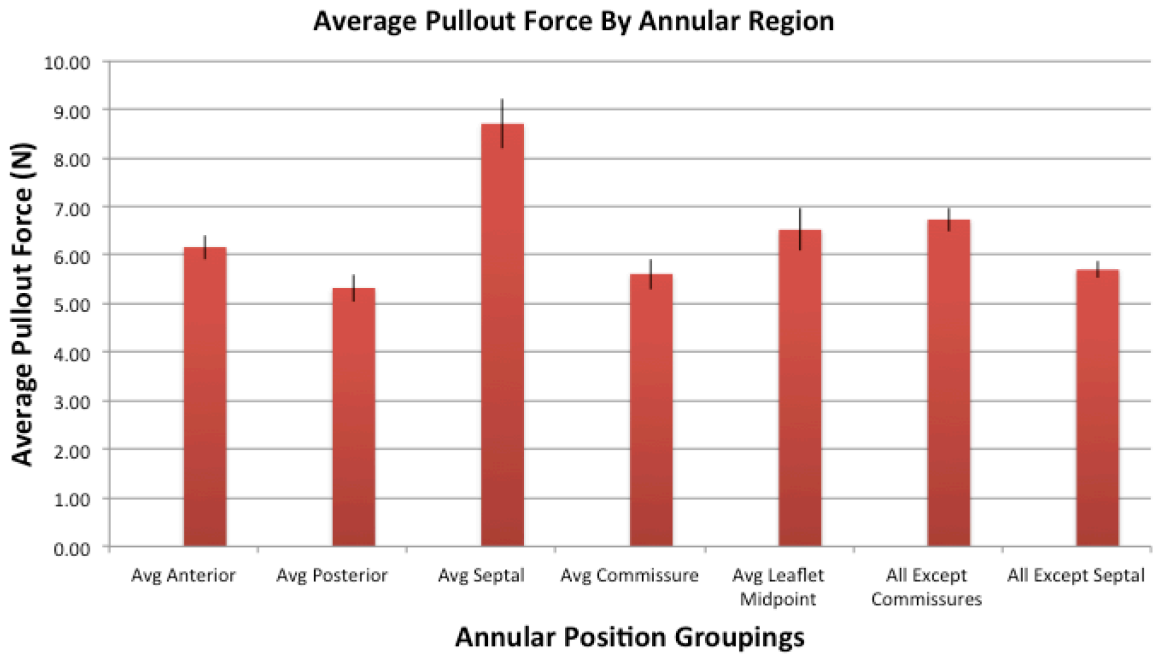

Figure 4.2. Average Pullout Forces By Annular Region. Position groupings of interest were chosen for comparison. The subgroups identified are graphed with their respective standard error bars.

The average leaflet midpoint positions (figure 4.2) were found to be stronger than the average commissural positions (6.52 ± 2.89, vs. 5.61 ± 2.13, $p<0.0082$). The posterior leaflet was found to be the weakest region around the tricuspid annulus (5.32 ± 1.90) and pullout force was found to be greatest at the septal annular region (8.70 ± 3.41, vs. 5.70 ± 1.94 at all other positions, $p<0.0001$).

T-Test Comparison	p-value
Septal vs. Anterior	<0.0001
Septal vs. Posterior	<0.0001
Anterior vs. Posterior	0.0293
Midpoint vs. Commissure	0.0082
Septal vs. All Other	<0.0001
Commissure vs. All Other	0.0163

Table 4.3. Unpaired t-test Comparisons of Tricuspid ROI's. Significant differences in the suture pullout forces necessary for dehiscence were found between all of the compared regions. The greater of the two in each pairwise comparison is named first in the table.

Table 4.3 shows significant differences in the pullout forces found between the septal region and all other groupings of positions tested.

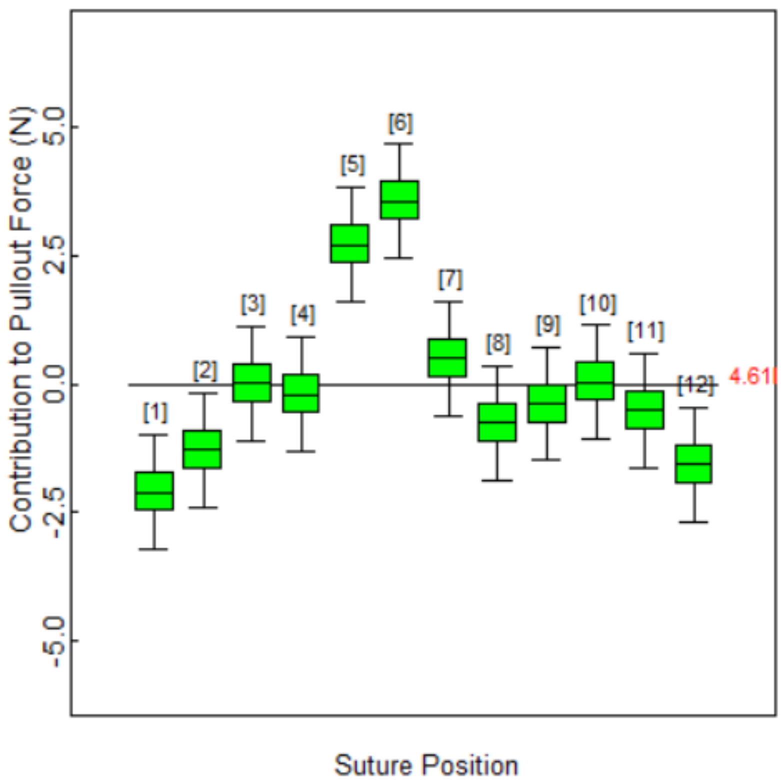

Figure 4.4. Box and Whisker Plot of Pullout Forces By Position. 95% confidence intervals for the change in force from the average across all positions owing to each specific position. Overlapping whiskers among any two positions indicate that their difference was not statistically significant (p>0.05), as determined by ANOVA.

Figure 4.4 allows for multiple comparisons among all twelve positions by ANOVA. The figure shows 95% confidence intervals, and establishes positions 5 and 6 as each having significantly higher pullout force than every other position. Positions 1 and 12 fell entirely below the average (no point across the 12 valves exceeded the average). A trend can be visualized in figure 4.4 around the circumference of the valve. Clockwise, pullout forces were highest at the septal region, then gradually decreased towards a minimum at position 1, then gradually increased towards position 6.

Collagen Characterization Results

The average pixel densities of non-specific fibers (red) were higher than those of collagen (green) across all 6 images of all 4 valves, underscoring the fact that load-bearing collagen constitutes a minority of the annulus tissue as a whole. The data was normalized to the septal leaflet (position 6) and a series of one-sample t-tests were used to test for significance; the normalized sample means were compared to the hypothetical mean of 1 for the septal leaflet.

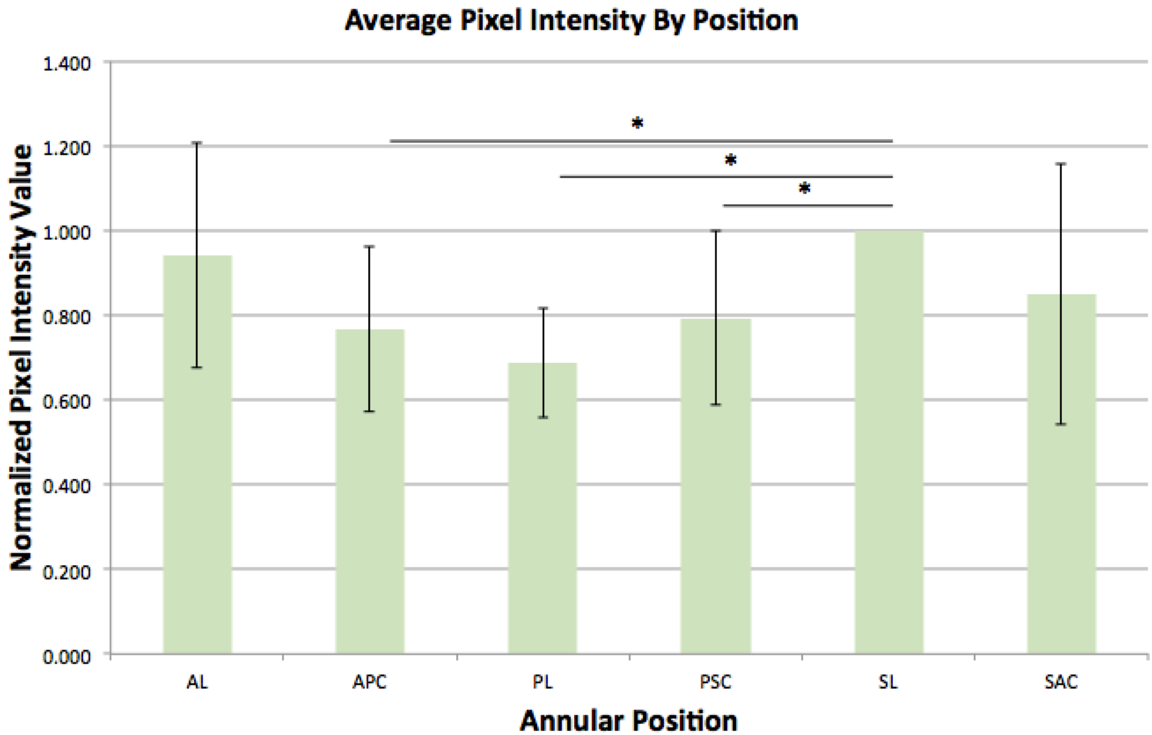

Figure 4.5. Normalized Pixel Intensities for Collagen by Position (mean ± SE). The septal leaflet had the highest average collagen pixel intensity overall (normalized mean of 1.00) and the posterior leaflet showed the lowest collagen pixel intensity (normalized mean of 0.69 ± 0.18). * = $p < 0.05$.

Significance was established (figure 4.5) between the septal leaflet midpoint and anterior-posterior commissure ($p = 0.0306$), between the septal leaflet midpoint and posterior leaflet midpoint ($p = 0.0393$), and between the septal leaflet midpoint and the posterior-septal commissure ($p = 0.462$).

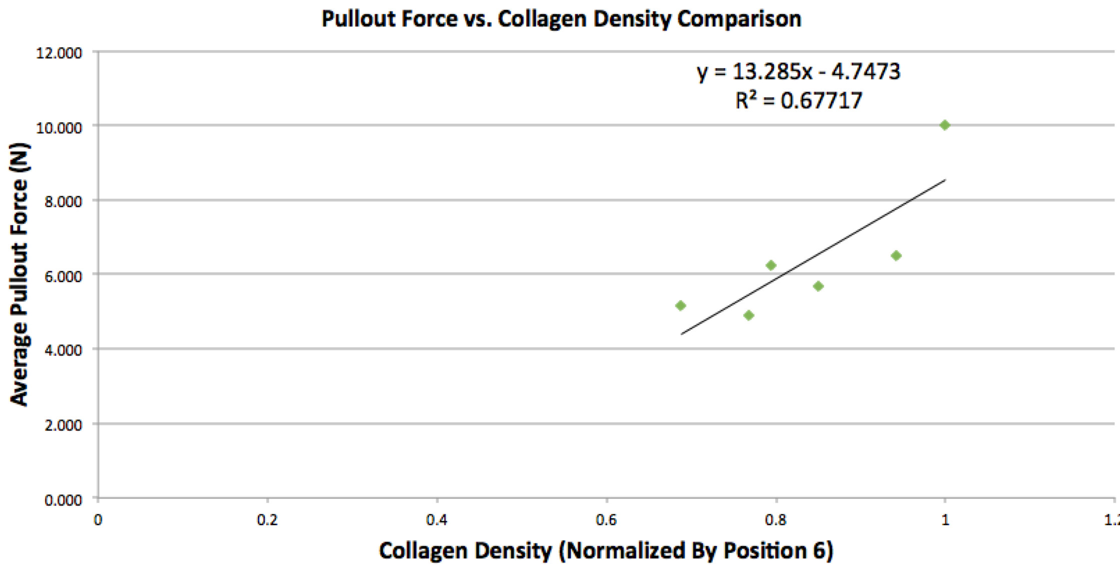

Figure 4.6. Correlation of Collagen Content and Pullout Force by Position. The points graphed are the 6 positions used for both studies. The collagen data has been normalized to the septal leaflet midpoint.

Figure 4.6 shows a direct comparison between the two experiments performed. The leftmost point is the posterior leaflet midpoint and the rightmost point is septal leaflet midpoint. An R^2 value of 0.68 was established, and a trend in increasing collagen density to increasing pullout force can be visualized. A trend was not observed between suture pullout force and myocardium density ($R^2 < 0.01$).

CHAPTER 4

DISCUSSION

Implications of Results

Annuloplasty rings used to treat FTR are implanted with sutures, which have the potential to dehisce once subjected to contractile forces. This study aimed to understand the mechanism of this dehiscence to support development of new ring designs and/or implantation techniques that minimize its occurrence. Clinical review showed that TV annuloplasty rings were found to dehisce most around the septal region[14], which motivated the hypothesis that the lowest pullout forces and lowest collagen content are found near the septal region of the annulus. Surprisingly, the opposite was observed; this region showed the strongest holding strength in this study. While not necessarily contradictory, these findings are counterintuitive. In combination with the clinical observation of more frequent dehiscence in this region, these data suggest it likely experiences significantly higher contractile forces *in vivo*.

The collagen content of the valve was visually observed to lie most densely at the endocardial surface of the annulus (figure 3.3). Sutures are inserted 1-2mm into the tissue, past the endocardial layer of collagen (<1mm thickness) (figure 3.3). Non-specific fibers, likely myocardium, make up the inner portion, where the final depth of an implanted suture would lie. For dehiscence to occur an implanted suture must tear through both the myocardium-rich and the collagen-rich layers; variation in collagen density across the circumference of the valve directly correlates (figure 4.6) to the differences in holding strength observed across the TV ($R^2 = 0.68$). No such correlation was observed between the myocardium density and pullout force across the annulus ($R^2 < 0.01$).

As cardiac contraction forces pull on collagen-dense regions via a suture, viscoelastic soft tissue strains in response; however, more rigid structures are not as compliant. Stress-strain curves for soft tissue demonstrate an exponential shape, indicating a greater initial compliance.[24] The rigid right fibrous trigone (figure 1.1) anchors septal tissue in place, reducing the compliance of the region. This consequently leads to higher tissue stiffness in this region more quickly. Sutures undergo higher tension when pulling on tissue less inclined to strain (figure 4.6), motivating the theory that the high forces necessary for dehiscence occur at this position during normal cardiac function.

For comparison, an *in vivo* study of the undersized annuloplasty suture forces at the mitral position found sutures at the right fibrous trigone to experience the highest cyclic loading of any position.[19] A similar phenomenon is hypothesized to occur on the side of this trigone facing the tricuspid valve. However, at the tricuspid position, these forces may be even greater still. This may explain the near exclusive clinical observation of dehiscence in the TV at this position. Mechanistically, the contribution of right ventricular contraction on a device attached to the mitral annulus is likely lesser than the contribution of left ventricular contraction on a device attached to the tricuspid annulus. This phenomenon may further intensify the forces acting on the tricuspid septal annular sutures meant to keep annuloplasty rings stable.

In the mitral valve, it appears that the posterior annular tissue has the lowest holding strength, and clinically, dehiscence occurs predominantly at this region. The weaker tissue in this valve is likely bearing more of the load. A more asymmetric distribution of the suture force around the annular circumference may be advantageous. In contrast, the TV likely has the strongest region bearing too much of the load. The proportion of the load being supported here may be more than ideal, placing the septal annulus at risk for suture dehiscence. A less asymmetric distribution of the suture force may be advantageous to remove the load from the septal tissue. These findings, in parallel with the suture pullout data collected from this study, lead to the belief that an *in vivo* analysis of a the cyclic forces acting on an undersized tricuspid annuloplasty ring would reveal tensions necessary to induce dehiscence. A live animal model is necessary to validate this potential proposed mechanism.

New techniques in development for device implantation present unique challenges for annular anchoring. Emerging technologies such as Mitralign[25] and Cardioband[26] take unique approaches to anchoring devices without conventional sutures. These unique approaches include the use of pledgets, screws and other mechanisms. These devices are typically being developed initially for the mitral valve, but transitions toward TV applications have begun.[25,26] This places an unprecedented importance on understanding the mechanical strength of the tricuspid annulus. As this device evolution process continues, the unique force dynamics associated with each new annular anchoring method must be characterized**.** The results of this study provide designers of these procedures with a foundation that anchoring mechanisms should be developed to account for the variable load-bearing capabilities of regions across the TV annulus. While the septal annulus may have the highest pullout force observed, this region should not necessarily be responsible for carrying a significant load. Such efforts to understand the tricuspid annulus and the anchoring potential of new technologies will help to improve the quality of post-procedural patient outcomes.

Limitations

The autofluorescence analysis performed did not discern between different collagen types. Type I collagen specifically provides resistance to tension[17]; however, if the collagen observed in this study was not primarily type I, then the causality of the variable holding strengths across the TV annulus would be subject to further investigation.

The ovine tissue used in this experimentation does not necessarily represent the tissue present in diseased, human valves. Prior to experimentation, the tissue had entered rigor mortis and started to decay. To minimize this, all suture pullout testing was performed within 2 weeks of attaining fresh hearts. Although healthy tissue was used in this study, the results obtained can be referred to as a baseline when exploring diseased tissue. Experimentation on regurgitant human TV's would provide a valuable next step in translating this work to practical applications.

The results from this study can be compared to the mitral valve[19], but are limited in their applications. The highest pullout forces were observed at the septum in this experiment, but testing of the mitral annulus at this same region found lower holding strengths. This inconsistency may be due to changes in the collagen matrix across different sides of the septum. Variability in collagen content cannot be assessed through a comparison of the two studies due to the different acquisition settings used for data collection. While variations in trends observed may be present, this study may not fully explain the implications of the differences.

CHAPTER 5

FUTURE WORK

The future direction of this work should include designing an animal study to record the forces that the heart experiences around the tricuspid annulus during cyclic contractions, as has been performed for the mitral valve.[18] This study would provide significant insight as to why dehiscence occurs most often at the region where, based on this study alone, it should least likely occur. An annuloplasty ring equipped with 12 force transducers would record *in vivo* measurements, and the results would be analyzed against data obtained from this study. This may ultimately support the proposed mechanism of dehiscence. Minimizing the potential for dehiscence by optimizing the design of annuloplasty rings will lead to improved outcomes for patients receiving surgical intervention for FTR.

CHAPTER 6

CONCLUSIONS

An understanding of the forces necessary for tricuspid suture dehiscence represents an important first step toward its prevention. This study demonstrated that the strongest holding strength and the highest collagen content were both found at the septal region of the annulus, which is contrary to clinical observation of dehiscence primarily occurring at this region. This is likely due to higher contractile forces as well as reduced tissue compliance in this region. Before these findings can be applied to develop improved ring design/implantation techniques, this hypothesis must be assessed in a live animal model.

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VITA

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